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RESPIRATORY TRACT TUMORS IN SYRIAN HAMSTERS FOLLOWING INHALATION OF $Pu-ZrO_2$ PARTICLES*

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ABSTRACT

Inhalation of radionuclide-bearing particles remains one of the most intensely pursued problems concerning the nuclear industry. This route of entry is generally accepted as the most probable, in case of human exposure, with ingestion being the other prominent source of concern. Recent safety advances in areas surrounding operations involving radionuclides, although effective, have not profoundly alleviated the concern over potential hazards. Thus, many laboratory investigations, such as those reported here, continue to evaluate the possible consequences that may present health problems to the public domain.

Syrian hamsters of both sexes received either inhaled (INH) PuO_2/ZrO_2 particles, intravenous (IV) PuO_2/ZrO_2 microspheres, a combination of INH PuO_2/ZrO_2 particles and injected PuO_2/ZrO_2 microspheres or no radionuclides (controls). The INH particles and IV microspheres were tagged with γ-emitting ^{57}Co to facilitate whole body counting and establishment of retention curves. Total lung burdens ranged from 8 nCi to 143 nCi. Significant numbers of primary lung tumors (5-50% per group) were induced in those animals that received INH exposures. Additional α radiation administered via Pu-laden IV microspheres had little or no effect on tumor production or nonneoplastic, degenerative changes in the respiratory tract.

* Work performed under the auspices of US Department of Energy.

1. INTRODUCTION

While more is known about the toxicity of plutonium than most other hazardous agents (1), there is still a tremendous amount, as with most carcinogens, to be learned regarding its role in tumorigenesis. Our laboratory for several years has studied the effects of alpha-emitting PuO_2-ZrO_2 microspheres on the lungs of Syrian hamsters (2-5). These biologically inert ceramic spheres act as focal sources of alpha-radiation, "hot particles", in the pulmonary milieu. When injected into the jugular vein, they lodge quantitatively in the lung capillaries for the durations of the animals life spans. Regardless of the number of spheres injected, or their specific activities, they are not efficient tumor inducers despite the surrounding respiratory tract cells being subjected to massive amounts of alpha-radiation, in excess of 30,000 rad/yr in some cases. Tumor induction frequencies average less than 1% via this exposure mode. A significant number of tumors result only when enhancing agents are administered concurrently. For example, a single dose of 3 mg Fe_2O_3/ saline intratracheally (IT), following microsphere injection (33 nCi Pu = 2600 rad/yr), raised the tumor incidence from 5% (spheres alone) to 38% (6).

The alpha emitter ^{210}Po instilled IT is an extremely effective tumorifacient agent in the Syrian hamster lung (7,8) when followed by weekly saline instillations. Inhaled PuO_2 produced lung tumors in dogs (9) and rats (10-13). However, it has not been an efficient lung tumor inducer in hamsters. Extensive attempts in three laboratories to experimentally produce pulmonary neoplasms in this species by internally deposited PuO_2 uniformly resulted in negative results (14-16). This is particularly interesting in light of the rat's susceptibility to Pu-induced respiratory tract carcinogenesis (17).

In this presentation we report the induction of significant numbers of primary lung tumors in the Syrian hamster by inhaled PuO_2/ZrO_2 particles.

2. MATERIALS AND METHODS

Syrian hamsters were exposed to ^{238}Pu or ^{239}Pu alpha radiation when 100 days old. The animals were obtained when 4 to 6 weeks old from the Engle Laboratory Animals in Farmersburg, IN. They were housed two to a polycarbonate cage containing low-dust-factor aspen shavings which were suspended on aluminum shelves covered with spun polyester filters (DuPont #22 Spinbonded Polyester

Filter, E-I DuPont Co., Wilmington, DE). Cages and bedding were changed twice a week. The hampsters were fed a commercial stock diet (Teklad Hamster Diet®, Teklad Mills, Winfield, IA) and were given chlorinated water *ad libitum*.

After the conditioning period, when the hamsters were approximately 100 days old, they were assigned to one of the ten groups in Table 1, receiving either inhaled (INH) PuO_2/ZrO_2 particles, IV PuO_2/ZrO_2 microspheres, a combination of inhaled PuO_2/ZrO_2 particles and injected PuO_2/ZrO_2 microspheres or no treatment (controls). Animals which died accidentally during Pu administration were not included; thus, each group differed in size. Animals with combined INH and IV administrations received the injected spheres one week prior to the inhalation.

The animals receiving IV spheres were given either 20,000, 30,000, or 60,000 very uniform 10 µm diameter ZrO_2 ceramic microspheres containing varying amounts of PuO_2.

Details of microsphere production and plutonium incorporation are given elsewhere (3). To deliver the plutonium-laden ZrO_2 microspheres, hamsters were anesthetized by intramuscular injection of Ketamime (Ketaset®, Bristol Laboratories, Syracuse, NY), placed in dorsal recumbency, and either jugular vein exposed by surgical incision and blunt dissection after skin disinfection. After injection, the wounds were closed with 9mm wound clips (Autoclips®, Clay-Adams, New York City). Because the ZrO_2/PuO_2 microspheres had a high density, a rapidly pulsed dental cleaning device (Water-Pik®, Aqua Tec Corporation, Denver, CO) was used to inject the microspheres, suspended in 0.2 ml 0.15 M NaCl, into the isolated jugular vein (18). Using this procedure, the radioactivity remains quantitatively in the lung.

The inhalation chamber and aerosol generation system were essentially the same as those previously reported (19). The starting material in the nebulizer was ZrO_2 sol similar to that used in the process of manufacturing the microspheres for IV injection (3). The desired amount of $Pu(NO_3)_4$ was added to the sol plus a small amount of γ ^{57}Co-emitting tracer. The droplets were passed through a heating column at 900°C before entering the inhalation chamber and the hamsters were exposed "nose only" for 20 minutes.

The radiation doses to be presented were calculated from the ^{57}Co retention patterns (from whole-body counting) with time for individual animals, integrating beneath the lung retention curve to obtain a total microcurie-days exposure and hence the total energy that the animals absorbed in their lungs over their lifespans. This rad dose is proportional to the number of ergs per gram received by the entire

lung and no attempt was made to calculate a radiation dose delivered by individual particles to localized regions of the lung. The lung weights used were from data collected on control hamsters sacrificed at various times of age, and not upon the weight at death. The sacrifices for tissue distribution were performed on two hamsters each at 1, 2, 4, 8, 16, and 32 days post-exposure in groups A-D. It was established that the label (^{57}Co) remains with the ZrO_2 particles through the intramuscular (IM) injection of a resuspension of aerosol particles into a group of 10 hamsters, and following whole-body retention and tissue distribution at necropsy after 371 days post injection.

For scoring tumor incidence, all animals were checked two or three times daily for the duration of their life spans, moribund hamsters were killed and necropsied, and dead hamsters were necropsied as soon as possible. The respiratory tract was inflated via the trachea with 5 to 6 cm^3 of 10% neutral buffered formalin and the trachea ligated. The respiratory tract was removed enbloc, fixed in 10% neutral buffered formalin, and counted for radioactivity with twin sodium iodide crystals.

The five lung lobes were separated after fixation, processed by standard methods, and routinely stained with hematoxylin and eosin. The lungs were also examined autoradiographically for alpha tracks.

3. RESULTS

3.1 Microspheres and Inhaled Particles

When serial sections of the lungs from animals in Groups A, C, D, G, and H were examined microscopically, the microspheres were distributed randomly throughout the capillary bed. The microspheres did not in themselves elicit any inflammatory reaction as long as they remained static in the capillaries. Slight foreign body tissue reactions (focal aggregations of alveolar macrophages) were seen only when a microsphere was extruded into an alveolar space - an uncommon occurence.

The aerosol particles were generally smooth and spheroid and had activity median aerodynamic diameters (AMAD's) of 1.5-2.0 um with σ_g's (geometric standard deviations) of ~2. The aerosols were consistent from run to run and did not appear to bear any relationship to the use of ^{238}Pu or ^{239}Pu as the radiation source due to the small amount in each particle (less than 1% by weight). The ^{238}Pu was utilized to attain a higher radiation dose for a small total amount of total plutonium as related to their isotopic half-lives.

The whole body burdens from the hamsters in Group I were plotted to determine the type of distribution at various times post inhalation (Figure 1). The total retention of the aerosol is shown in Figure 1 as determined by whole body counting of the ^{57}Co tag over a period of 425 days post exposure. After rapid initial drop due to a combination of rapid excretion from the upper respiratory tract and loss of surface contamination, the retention beyond 30 days approached a single exponential function with a half life of 130 days. Allowing for the physical decay half life of 271 days leaves a biological half life of 250 days.

3.2 Lifespans

The survival data for all the animals are included in Table I. With one exception (Group G), males lived longer than females in both experimental and control hamsters. This was particularly evident in groups B-F. The most dramatic life shortening compared to controls (E, F, & J) occurred in groups G, H, & I - the only ones receiving large doses via inhalation and containing hamsters with a significant number of lung tumors. Groups B & C, which received low doses via inhalation, had median lifespans post exposure that were only slightly lower from those of controls.

Figure 2 shows for Groups G, H, and I, the initial lung burdens plotted against survival time. Each point records the death of an individual hamster and the presence or absence of tumors at death is indicated by the plotting symbol. The initial value of the long-term component of the lung burden is used to measure the majority of the radiation dose to the lung. A major portion of the higher activity at early times was external contamination or was in transit through the gut.

The expected increase of survival time with decreasing lung burden is clearly evident. A minimal time to tumor appearance of about 100 days can also be deduced. It is notable that tumors were virtually absent from animals receiving less than 50 nCi even though many of them had normal lifespans. This form of data presentation preserves all of the available information about dose, time, and incidence and permits later analysis for the averaged parameters. Note that this figure suggests an increasing induction time and a decreasing total incidence with declining lung burden.

3.3 Neoplastic and Preneoplastic Pulmonary Lesions

The incidence and type of pulmonary tumors is included as Table II while non-neoplastic lesions of the lung are given in Table III. The highest frequency of lung tumors (50%) occurred in Group I animals which received mean lung burdens of

[illegible] nCi ^{238}Pu via inhalation only. Group G with mean total lung burdens of [illegible] nCi ^{238}Pu (56 nCi via 20,000 microspheres IV plus 87 nCi via inhalation) had a 40% lung tumor incidence. Twenty-eight percent of the hamsters in Group H developed pulmonary tumors. They had mean total lung burdens of 129 nCi ^{238}Pu achieved with 53 nCi via 20,000 microspheres IV and 76 nCi via inhalation. The predominant tumors in G, H, and I were adenomas; however, adenocarcinomas were common in all three groups. The only squamous cell (epidermoid) carcinomas found in this study were in Group I.

The vast majority (90%) of all tumors were peripheral, i.e., arising from the bronchial tree in or distal to secondary bronchi with the notable exception of Group I's squamous cell carcinomas which originated from bronchial epithelium in hilar portions of the lung. Histologically, the adenomas were comprised of polygonal, well differentiated cells with eosinophilic cytoplasm and uniform round-ovoid basophilic nuclei. These tumors were well-circumscribed and usually associated with bronchi or bronchioles suggesting that they arose from bronchial or bronchiolar epithelial cells. The adenocarcinomas were characterized by irregularly shaped cells with granular eosinophilic cytoplasm, pleomorphic, basophilic nuclei that formed poorly circumscribed, expansive tumor masses. Mitotic activity was not a common feature. These tumors usually occupied large portions of the lung, so it was not possible to precisely pinpoint a locus of origin. Due to their similarity to the adenomas, it is likely that they also were derived from bronchial or bronchiolar epithelium. The three squamous cell carcinomas were well-differentiated with prominant intercellular bridges and keratin formation. They undoubtedly arose from bronchial epithelial cells as each was associated with a main-stem bronchus. Seventy percent of all the tumors were in the left lobe of the lung with the remaining tumors indicating even distribution throughout the other four principal lobes. Fibrosis was highest in Groups G, H, and I (Table III) which also had the highest numbers of tumors indicating that mesenchymal as well as epithelial cells were profoundly disturbed by inhaled PuO_2/ZrO_2. Likewise, these three groups had the highest incidences of bronchiolar adenomatoid lesions (BAL) (Table III), proliferations of terminal bronchiolar epithelium into alveolar spaces.

3.4 Radiation Doses and Tumor Incidences

As is evident from Figure 2, individual hamsters acquired very different lung burdens as a result of biological variability and nonuniform distribution of the aerosol within the exposed chamber. However, all the hamsters were

measured individually to determine their actual burdens over the course of the experiment. It is, therefore, possible to regroup the animals into a number of narrower dose ranges as shown in Table IV. The rows of the table correspond to the selected intervals of the inhaled lung burden only and the columns to the three levels of microsphere burdens (the later burdens were precisely regulated and pre-determined to with about ± 20%). Inspection of Table IV leads to the somewhat surprising conclusion that tumor incidence was independent of microsphere burden and depended only on the inhaled lung burden. There is certainly no evidence of synergism or enhancement. The statistical errors are too large to permit accurate determination of the shape of the dose-response curve, but the trend in the final column is clearly monotonic with respect to inhaled lung burden.

4. DISCUSSION

The study of radiation-induced respiratory tract carcinogenesis in our laboratory initially focused on the so-called "hot particle" issue. Ceramic PuO_2/ZrO_2 microspheres given IV were used as focal sources of alpha radiation in the lung. Primary tumor production from this means of selective exposure was essentially zero and provoked the concern that this species was perhaps not a desirable indicator of plutonium-induced carcinogenesis. To test this premise, another insult mode was utilized, i.e., the deposition of PuO_2/ZrO_2 particles in the form of an inhaled polydispersed aerosol. Thus, two factors were introduced that varied from the "hot particle" concept; namely, the aerosol particles were much smaller and more numerous than the microspheres and furthermore, were in motion and actively transported out of the lung. Both of these factors greatly reduced localized concentration of dose and resulted in a much more diffuse deposition of energy. However, they do not differ in these respects from aerosols of PuO_2, which are also non-tumorogenic in hamster lung.

Those groups, A, E, F, and J that received microspheres without inhaled particles, had extremely low or a zero incidence of pulmonary neoplasms. This is in agreement with earlier work from our laboratory (5).

Interestingly, Group B, which received only 8 nCi ^{239}Pu via inhalation and Group C which was given 30,000 microspheres IV (49 nCi ^{239}Pu) plus 6 nCi inhaled ^{239}Pu, had lung tumor incidence of 12% and 5% respectively.

It is obvious from Table II that the major factor resulting in lung tumor growth and development in this study was the administration of ^{239}Pu or ^{238}Pu via inhalation. Apparently, microspheres containing ^{239}Pu or ^{238}Pu lodged intra-

vascularly had little influence in tumorigenesis or fibrosis. Bronchiolar adenomatoid lesion (BAL) and squamous metaplasia were prevalent in most animals. Further, as this lesion was also found in hamsters that received no radiation (Groups E, F, and J) it is difficult to relate this change as definitively being preneoplastic. Squamous metaplastic changes (Table III) were observed in all groups except B, D, and J and did not correlate with either radiation doses or tumor incidences.

The observation that female hamsters had shorter lifespans than males, regardless of treatment in this study, was interesting and is in agreement with the published findings of Bernfield (20) and Redman and Hobbs (21).

Results of this study were surprising in that the inhalation of PuO_2 particles alone had not indicated a tumorigenicity in the Syrian hamster in our laboratory, nor in at least two other laboratories (14-16). The obvious questions now being answered through further study, center about the reproducibility of the results and the possible adjunctive role of the ZrO_2 matrix in tumor formation. This latter factor is a real enigma because of the presumed biological inactivity of a ZrO_2 particle, as evidenced by the lack of foreign body reactions or other lesions when the ZrO_2 particles are administered alone without radioactivity. Experiments are in progress substituting thoria and urania for zirconia to determine whether a similar effect exists. These materials are of interest because, in addition to being chemically similar to ZrO_2, they compose the fuel elements of breeder reactors. Results of these further investigations are presently becoming available.

TABLE I

Experimental Design for Studies with (^{238}Pu-Zr)O_2 or ^{239}Pu-Zr[illegible]. Injected IV into or Inhaled by Syrian Hamsters.

Gp	Number of Hamsters			Initial Pu Lung Burdens				Mid or Effective Plateau Post Exposure	
	MALE	FEMALE	ISOTOPE	Mean # Spheres Injected	Injection (nCi)	Inhalation (nCi)	Total (nCi)	Males	Females
	26	27	^{239}Pu	60000	117	0	117	399	[illegible]
	17	26	^{239}Pu	0	0	8	8	467	[illegible]
	16	24	^{239}Pu	30000	49	6	55	528	230
	23	22	--	30000	0	0	0	532	368
	34	21	--	0	0	0	0	547	239
	23	21	--	0	0	0	0	582	357
	23	27	^{238}Pu	20000	56	87	143	198	234
	30	30	^{238}Pu	20000	53	76	129	268	252
	20	24	^{238}Pu	0	0	101	101	176	171
	14	31	--	0	0	0	0	447	445

does not include serially killed animals out to 32 days postexposure.

estimated from long term lung retention kinetics (alveolar burden). The two digits used n these numbers were determined from retention equations, but it is obvious from such echniques that rounding off is a sufficiently accurate accounting of the actual lung burdens e.g. 87 nCi could as accurately be reported as 90 nCi).

Group D received ^{57}Co labeled ZrO_2 and IV aerosol particles.

Group F received unlabled ZrO_2 aerosol particles.

TABLE II

Pulmonary Neoplasms

Group	Number of Tumor-Bearing Animals Divided by Number of Animals	Number with Multiple Tumors Divided by Number of Animals	Adenoma	Adeno-Carcinoma	Squamous Cell Carcinoma
A	1/53 (2%)	0/1 (0%)	1/1 (100%)	--	--
B	5/43 (12%)	0/5 (0%)	5/5 (100%)	--	--
C	2/40 (5%)	0/2 (0%)	2/2 (100%)	--	--
D	0/45 (0%)	--	--	--	--
E	1/55 (2%)	0/1 (0%)	1/1 (100%)	--	--
F	0/44 (0%)	--	--	--	--
G	20/50 (40%)	4/20 (20%)	12/20 (60%)	8/20 (40%)	--
H	17/60 (28%)	3/17 (18%)	11/17 (65%)	6/17 (35%)	--
I	22/44 (50%)	4/22 (18%)	10/22 (45%)	9/22 (41%)	3/22 (14%)
J	0/45 (0%)	--	--	--	--

TABLE III

Non-Neoplastic Pulmonary Lesions*

Group	Fibrosis	Bronchiolar Adenomatoid Lesions (BAL)	Squamous Metaplasia
A	5/52 (10%)	24/52 (46%)	1/52 (2%)
B	3/38 (8%)	4/38 (11%)	--
C	1/38 (3%)	7/38 (18%)	1/38 (3%)
D	--	1/45 (2%)	--
E	--	5/44 (11%)	1/44 (2%)
F	2/44 (5%)	5/44 (11%)	1/44 (2%)
G	24/30 (80%)	18/30 (60%)	4/30 (13%)
H	16/43 (37%)	11/43 (26%)	1/43 (2%)
I	17/22 (77%)	12/22 (55%)	2/22 (9%)
J	--	1/45 (2%)	--

* In non-tumor-bearing animals.

TABLE IV

TUMOR INCIDENCE

nCi Lung Burden (40-60 day)	G		H		I		All Experiments
	#Tumor Bearing ; #Animals	Malignant (all times)	#Tumor Bearing ; #Animals	Malignant (all times)	#Tumor Bearing ; #Animals	Malignant (all times)	
<25	0/0	0/0	0/0	0/0	0/1	0/0	0/1
25-50	0/0	0/0	0/0	0/0	0/6	0/0	0/6
50-100	1/10	0/1	3/16	2/5	2/14	1/3	9/40 - 23 + 8%
100-125	4/17	1/4	5/18	2/7	9/16	7/11	23/51 = 43 + 9%
125-150	10/18	5/12	3/14	0/3	6/8	2/6	21/40 = 52 + 11%
150-175	2/9	0/2	2/4	0/2	4/4	1/4	8/17 - 47 + 17%
>175	3/5	2/4	4/6	2/4	1/1	1/1	9/12 = 75 + 25%

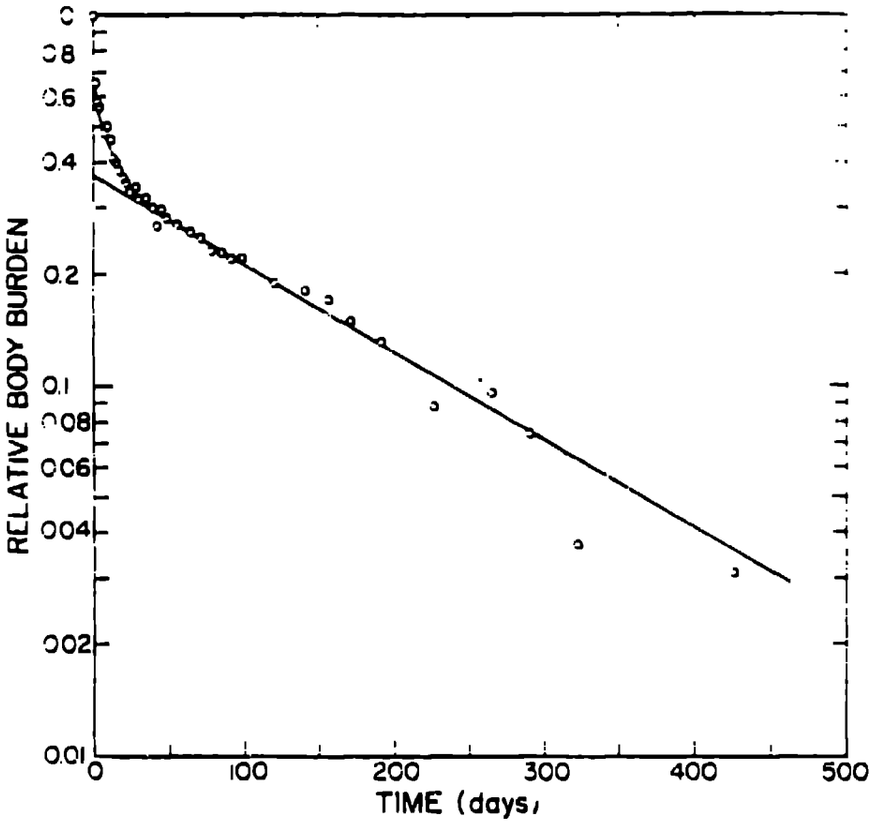

FIGURE 1

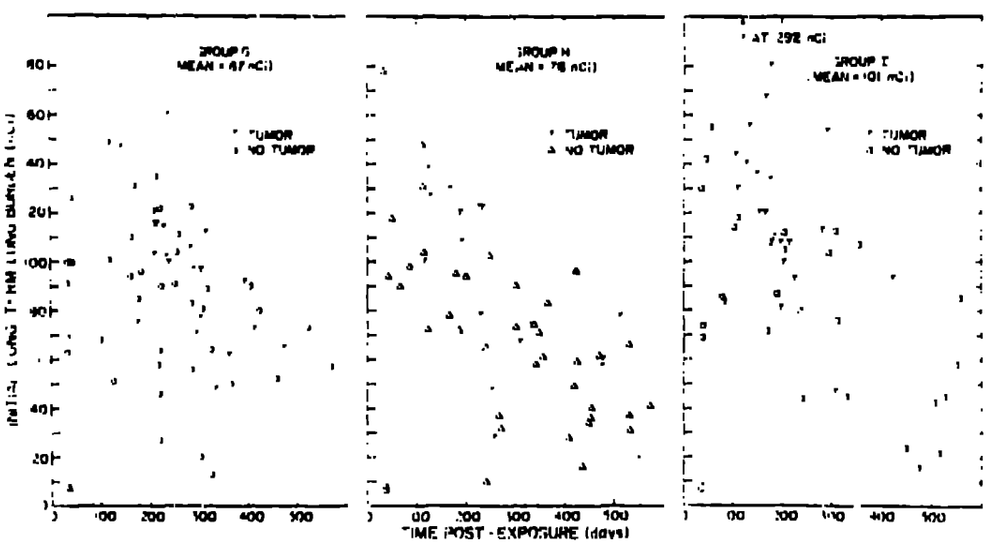

FIGURE 2

FIGURE LEGENDS

FIGURE 1:

Relative Body Burdens plotted versus time for the animals in Group I.

FIGURE 2:

Initial Long Term Lung Burdens (nCi) plotted versus time post-Exposure for Groups G, H and I.

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